

# PATENT COOPERATION TREATY

## PCT

### NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 22 August 2000 (22.08.00)	
<b>International application No.</b> PCT/EP99/09843	<b>Applicant's or agent's file reference</b> Le A 33 324-WO STO
<b>International filing date (day/month/year)</b> 13 December 1999 (13.12.99)	<b>Priority date (day/month/year)</b> 16 December 1998 (16.12.98)
<b>Applicant</b> ALBERS, Markus et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
06 July 2000 (06.07.00)

☐ in a notice effecting later election filed with the International Bureau on:  
\_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p style="text-align: center;"><b>The International Bureau of WIPO</b>                  34, chemin des Colombettes                  1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p style="text-align: center; font-weight: bold;">Nestor Santesso</p> <p>Telephone No.: (41-22) 338.83.38</p>
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PCT

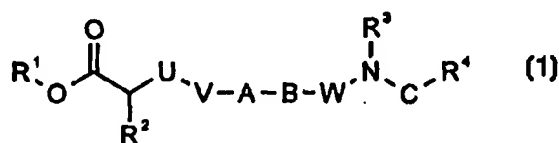
WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : C07C 311/19, 275/42, 311/10, 311/47, C07D 213/40, 213/75, 235/30, A61K 31/18, 31/44, 31/4184, A61P 35/00, 19/10, 27/02		A1	(11) International Publication Number: <b>WO 00/35864</b>  (43) International Publication Date: 22 June 2000 (22.06.00)
(21) International Application Number: PCT/EP99/09843 (22) International Filing Date: 13 December 1999 (13.12.99)  (30) Priority Data: 09/213,381 16 December 1998 (16.12.98) US  (71) Applicant (for all designated States except US): BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE).  (72) Inventors; and (75) Inventors/Applicants (for US only): ALBERS, Markus [DE/DE]; Am Plankengarten 24, D-51061 Köln (DE). URBAHNS, Klaus [DE/DE]; Pahlkestrasse 3, D-42115 Wuppertal (DE). VAUPEL, Andrea [DE/DE]; Birkenhöhe 9, D-42113 Wuppertal (DE). HÄRTER, Michael [DE/DE]; Maushäuschen 15, D-42489 Wülfrath (DE). SCHMIDT, Delf [DE/DE]; Am Eckbusch 55b, D-42113 Wuppertal (DE). STELTE-LUDWIG, Beatrix [DE/DE]; Görtzheide 10f, D-52489 Wülfrath (DE). GERDES, Christoph [DE/DE]; Christian-Hess-Strasse 81, D-51373 Lev- erkusen (DE). STAHL, Elke [DE/DE]; Reutherstrasse 124, D-51467 Bergisch Gladbach (DE). KELDENICH,		Jörg [DE/DE]; Damaschkeweg 49, D-42113 Wuppertal (DE). BRÜGGEMEIER, Ulf [DE/DE]; Leysiefen 20, D-42799 Leichlingen (DE). LUSTIG, Klemens [DE/DE]; Krummacherstrasse 179, D-42115 Wuppertal (DE).  (74) Common Representative: BAYER AKTIENGE- SELLSCHAFT; D-51368 Leverkusen (DE).  (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: NEW BIPHENYL AND BIPHENYL-ANALOGOUS COMPOUNDS AS INTEGRIN ANTAGONISTS



(57) Abstract

The present invention relates to biphenyl and biphenyl-analogous compounds, their preparation and use as pharmaceutical compositions, as integrin antagonists and in particular for the production of pharmaceutical compositions for the treatment and prophylaxis of cancer, arteriosclerosis, restenosis, osteolytic disorders such as osteoporosis and ophthalmic diseases. The compounds according to the invention have formula (1) wherein R<sup>1</sup>, R<sup>2</sup>, U, V, A, B, W, R<sup>3</sup>, C and R<sup>4</sup> have the meaning as defined in the claims.

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/09843

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/19 C07C275/42 C07C311/10 C07C311/47 C07D213/40  
C07D213/75 C07D235/30 A61K31/18 A61K31/44 A61K31/4184  
A61P35/00 A61P19/10 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 00395 A (MERCK PATENT) 8 January 1998 (1998-01-08) cited in the application page 1 -page 2 ---	1, 19, 20
A	DE 195 48 709 A (MERCK PATENT) 3 July 1997 (1997-07-03) the whole document ---	1, 19, 20
A	WO 97 36859 A (RICO JOSEPH G ; SEARLE & CO (US); YU STELLA S (US); CHEN BARBARA B) 9 October 1997 (1997-10-09) page 4 -page 10 --- -/-	1, 19, 20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the International filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 May 2000

Date of mailing of the international search report

06/06/2000

Name and mailing address of the ISA

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Authorized officer

English, R

# INTERNATIONAL SEARCH REPORT

Int. onal Application No

PCT/EP 99/09843

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 99 36393 A (TANABE SEIYAKU)  22 July 1999 (1999-07-22)  examples 23, 27-29, 46-48, 58, 59,  114-116, 122, 132-134, 157, 160-162, 164,  243-265, 319, 323, 324, 353-357  page 9 -page 11</p>	1, 19

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/09843

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9800395	A	08-01-1998	DE 19654483 A	02-01-1998
			AU 3343097 A	21-01-1998
			BR 9709953 A	10-08-1999
			CA 2259224 A	08-01-1998
			CZ 9804249 A	17-03-1999
			EP 0907637 A	14-04-1999
			NO 986090 A	23-12-1998
			PL 330915 A	07-06-1999
			SK 176898 A	07-05-1999
DE 19548709	A	03-07-1997	AU 1301697 A	17-07-1997
			BR 9612201 A	13-07-1999
			CA 2241149 A	03-07-1997
			CZ 9801951 A	11-11-1998
			WO 9723451 A	03-07-1997
			EP 0879227 A	25-11-1998
			JP 2000502664 T	07-03-2000
			NO 982907 A	22-06-1998
			PL 327185 A	23-11-1998
			SK 78398 A	04-11-1998
WO 9736859	A	09-10-1997	AU 2536097 A	22-10-1997
			CA 2250698 A	09-10-1997
			EP 0891325 A	20-01-1999
			US 5952381 A	14-09-1999
WO 9936393	A	22-07-1999	AU 2458499 A	02-08-1999

## PATENT COOPERATION TREATY

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>Le A 33 324-WO STO</b>		<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. <b>PCT/EP99/09843</b>	International filing date (day/month/year) <b>13/12/1999</b>	Priority date (day/month/year) <b>16/12/1998</b>	
International Patent Classification (IPC) or national classification and IPC <b>C07C311/19</b>			
Applicant <b>BAYER AKTIENGESELLSCHAFT et al.</b>			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input checked="" type="checkbox"/> Certain documents cited</li> <li>VII <input type="checkbox"/> Certain defects in the international application</li> <li>VIII <input checked="" type="checkbox"/> Certain observations on the international application</li> </ul>			
Date of submission of the demand  <b>06/07/2000</b>		Date of completion of this report  <b>09.01.2001</b>	
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>		Authorized officer  <b>Butkowskyj-Walkiw, T</b>  <b>Telephone No. +49 89 2399 8594</b> 	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/09843

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

**Description, pages:**

1-324 as originally filed

**Claims, No.:**

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☐ the claims, Nos.:  
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP99/09843

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

**2. Citations and explanations  
see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

**V.**

In the light of the documents cited in the search report the subject-matter of the present claims 1-22 can be considered as being novel (Art. 33(2) PCT).

However, the subject-matter of the present claims 1-22 is open to objection as to lack of inventive step (Art. 33(3) PCT) as the object of the present application, namely to provide compounds which exhibit a high activity as integrin antagonists and in particular against the  $\alpha_v\beta_3$  and/or the  $\alpha_v\beta_5$  receptor already has been suggested by D1 (WO-A-97/36859; pages 4-10) and D2 (DE-A-195 48 709; claims 1-10) in a very similar manner.

**VI.**

The current assessment is based on the assumption that the present priority is validly claimed. The cited document WO-A-99/36393 is therefore not considered art of the prior art for the purposes of Art. 33(2)(3) PCT pursuant to Rule 64(3) PCT.

**VIII.**

Claim 1 is too broad in scope and not fully supported by the present specification (Art. 6 PCT). Said claim contains an enormous amount of compounds and it is doubtful whether all of them solve the problem underlying the present application.

Terms like "alkyl" or "cycloalkyl" without any indication of carbon atoms are unclear.

The last paragraph on page 324 implies that the extent of protection may be expanded in some vague and not precisely defined way.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>Le A 33 324-WO ST0</b>	<div style="display: flex; justify-content: space-between;"> <div style="text-align: center;"> <b>FOR FURTHER ACTION</b> </div> <div style="font-size: small;">             see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.           </div> </div>	
International application No. <b>PCT/EP 99/ 09843</b>	International filing date (day/month/year) <div style="text-align: center;"><b>13/12/1999</b></div>	(Earliest) Priority Date (day/month/year) <div style="text-align: center;"><b>16/12/1998</b></div>
Applicant  <b>BAYER AKTIENGESELLSCHAFT et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure N .

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

= \_\_\_\_\_  
☐ None of the figures.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/09843

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C311/19 C07C275/42 C07C311/10 C07C311/47 C07D213/40  
C07D213/75 C07D235/30 A61K31/18 A61K31/44 A61K31/4184  
A61P35/00 A61P19/10 A61P27/02

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 00395 A (MERCK PATENT) 8 January 1998 (1998-01-08) cited in the application page 1 -page 2 ---	1, 19, 20
A	DE 195 48 709 A (MERCK PATENT) 3 July 1997 (1997-07-03) the whole document ---	1, 19, 20
A	WO 97 36859 A (RICO JOSEPH G ; SEARLE & CO (US); YU STELLA S (US); CHEN BARBARA B) 9 October 1997 (1997-10-09) page 4 -page 10 --- -/--	1, 19, 20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search

25 May 2000

Date of mailing of the international search report

06/06/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3018

Authorized officer

English, R

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/09843

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 99 36393 A (TANABE SEIYAKU)  22 July 1999 (1999-07-22)  examples 23, 27-29, 46-48, 58, 59,  114-116, 122, 132-134, 157, 160-162, 164,  243-265, 319, 323, 324, 353-357  page 9 -page 11</p> <p style="text-align: center;">-----</p>	1, 19

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 99/09843

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
W0 9800395 A	08-01-1998	DE 19654483 A	02-01-1998
		AU 3343097 A	21-01-1998
		BR 9709953 A	10-08-1999
		CA 2259224 A	08-01-1998
		CZ 9804249 A	17-03-1999
		EP 0907637 A	14-04-1999
		NO 986090 A	23-12-1998
		PL 330915 A	07-06-1999
		SK 176898 A	07-05-1999
DE 19548709 A	03-07-1997	AU 1301697 A	17-07-1997
		BR 9612201 A	13-07-1999
		CA 2241149 A	03-07-1997
		CZ 9801951 A	11-11-1998
		W0 9723451 A	03-07-1997
		EP 0879227 A	25-11-1998
		JP 2000502664 T	07-03-2000
		NO 982907 A	22-06-1998
		PL 327185 A	23-11-1998
		SK 78398 A	04-11-1998
W0 9736859 A	09-10-1997	AU 2536097 A	22-10-1997
		CA 2250698 A	09-10-1997
		EP 0891325 A	20-01-1999
		US 5952381 A	14-09-1999
W0 9936393 A	22-07-1999	AU 2458499 A	02-08-1999